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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/726,752	12/02/2003	Ian Richard Buxton	PU4727US-1	6812

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EXAMINER	
RAMACHANDRAN, UMAMAHESWARI	
ART UNIT	PAPER NUMBER
1617	

MAIL DATE	DELIVERY MODE
05/29/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/726,752	BUXTON ET AL.	
	Examiner	Art Unit	
	Umamaheswari Ramachandran	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13 and 33-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13 and 33-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/4/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Election/Restrictions

Applicants' election of group IV, claims 13, 34-42 in the reply filed on Apr 4 2007 is acknowledged. Claims 1-12, 14-33, 43, 44 are withdrawn from consideration. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Thus the restriction requirement elected is made final. Claims 13, 34-42 are pending.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 13 is rejected under 35 U.S.C. 102(b) as being anticipated by Jao et al (U.S. 5,955,103).

Jao et al. teach a bioerodible dosage comprising a bioerodible polymer matrix comprising 1 mg to 1200 mg of an antiepileptic drug such as lamotrigine that delivers the said drug to a drug receptor at a rate of release controlled by the bioeroding polymer matrix thirty minutes to seven days (col. 9, lines 66-67, col. 10, lines 1-12).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claim 13 is rejected under 35 U.S.C. 102(e) as being anticipated by Nadkarni (WO 03/104192).

Nadkarni teach rapidly disintegrating multiparticulate controlled release formulations of lamotrigine or a pharmaceutically acceptable salt in a core to provide better control of blood plasma level (see Abstract).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 33-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nadkarni (WO 03/104192) in view of Staniforth (U.S. 5,004,614).

Nadkarni's teachings discussed as above. Nadkarni further teach a release rate controlling polymer such as poly(methyl methacrylate), poly(ethyl methacrylate) etc (see Abstract, p 6, lines 30-34) in the composition. The reference teaches that the dosage formulation comprises a rate controlling polymer membrane made up of pharmaceutically acceptable polymers such as hydroxypropylmethyl cellulose, polyvinylpyrrolidone, polymers of acrylic and methacrylic acid such as (p 6 lines 27-29). The reference teaches the addition of excipients, diluents such as microcrystalline cellulose, lactose and lubricants such as magnesium stearate (p 9 lines 24-25, p 10 ,line 8). The reference also teaches Eudagrit RL as a suitable polymer (p 31, lines 4-5). The reference further teaches the amount of polymer(s) to be used in forming the particles will be determined based on the amount of drug to be delivered, the drug release rate desired, and the size of the particles and the total amount of the particles including copolymer, filler, plasticizer, excipients and processing aids, are preferably in the range of 5% to 60% weight gain on the cores (p8, lines 9-15). The reference teaches that controlled release lamotrigine, which is designed to avoid excessive Cmax levels will produce lower plasma concentrations, which are reached over a longer period of time (p3, lines 6-7). Nadkarni teach the weight of lamotrigine as 51 % (900 g of lamotrigine added to provide 1750 g of controlled release particles, example 1), and the weight of release retarding polymer such as hydroxypropyl methyl cellulose to be 31% (545.5 g of the polymer added to provide 1750 g of controlled release particles, example 1). The reference teaches the weight of microcrystalline cellulose to be 57% by weight (493.5 g

added to total weight of 867.05 g, example 4) and the lubricants may comprise from 0.05 to 10 weight % of the formulation (p10, lines 1-15).

The reference does not teach the thickness of outer coating or outer coating with one or more orifices.

Staniforth teach a device for controlled release of an active agent, comprising a core comprising an active agent and a release modifying agent; and an outer coating covering said core, the thickness of said coating being adapted such that it is substantially impermeable to the entrance of an environmental fluid present in an environment of use and substantially impermeable to the exit of said active agent during a dispensing period, said coating including an orifice extending substantially completely through said coating but not penetrating said core and communicating from said environment of use to said core for allowing the release of said active agent into said environment of use, said orifice having an area from about 10 to about 60 percent of the face area of said device, the rate limiting step for the release of said active agent substantially being the exit of said active agent through said orifice via one or more of dissolution, diffusion or erosion of said active agent in solution or suspension (col.16, lines 1-24, claim 1). The reference further teaches the drug to be an active agent (col. 5, lines 54-56). The reference teaches diluents such as lactose, fructose etc (col. 5, line 4), magnesium stearate (0.25-5%) weight of the core as a lubricant (col. 5, line 19) and hydroxypropylmethyl cellulose for thick coatings of the polymeric materials (col. 6, lines 60-65). The reference teaches that the thickness of the coating necessary to provide results in accordance may be simply determined by one of ordinary skilled in the art via

the preparation of devices with differing coating thicknesses, performing dissolution tests in the devices without the inclusion of an orifice in the device, and choosing the coating thickness which does not allow the release of the active agent from the device during the desired duration of controlled release (col. 7, lines 3-13).

It would have been obvious to one of ordinary skill in the art at the time of the invention to make a sustained release formulation of lamotrigine with an outer coat covering said core impermeable to environmental fluids because of the teachings of Nadkarni and Staniforth. Nadkarni teaches that the advantage of controlled release of a drug is to provide therapeutically effective level of an agent for an extended period of time and longer period of pharmacological and diagnostic response and teaches sustained release formulation of lamotrigine. Staniforth teaches a different technique of controlled release formulation of drugs by adjusting the thickness of the outer coating so that it is substantially impermeable to the entrance of an environmental fluid present in an environment of use and substantially impermeable to the exit of said active agent during a dispensing period. Hence one of ordinary skill in the art would have been motivated to combine the teachings of Nadkarni with Staniforth to provide a sustained release formulation of lamotrigine with an outer coating that is impermeable to environmental fluid and impermeable to the exit of an active agent such as lamotrigine.

The reference does not teach a value for the thickness of the outer coat polymer as claimed in claims 38 and 39 of the instant application.

It would have been obvious to one of ordinary skill in the art at the time of the invention to make an outer coat of the formulation of lamotrigine with 0.05-0.30 mm of

mm of polymer. The motivation to do so is provided by Staniforth's teachings. The reference clearly teaches that the thickness of the coating necessary to provide results in accordance may be simply determined by one of ordinary skilled in the art via the preparation of devices with differing coating thicknesses, performing dissolution tests in the devices without the inclusion of an orifice in the device, and choosing the coating thickness which does not allow the release of the active agent from the device during the desired duration of controlled release (col. 7, lines 3-13). Hence one of ordinary skill in the art would have been able to adjust the thickness of the outer coat of the sustained formulation of lamotrigine by routine experimentation as Staniforth teaches the controlled release device having a core and an outer coating and the outer coating polymer materials and examples to make the formulation.

The reference does not teach that the outer coat may dissolve by 0.3-5 h after administration or when the surrounding pH exceeds 5.

It would have been obvious to one of ordinary skill in the art that the outer coat may dissolve when the surrounding pH exceeds 5 because the physiological pH is 6.8-7.4 and when lamotrigine is administered orally one can expect the dissolution of the outer coat in the stomach as the physiological pH exceeds 5. Also, One of ordinary skill in the art would be motivated to use the appropriate pH that would simulate in vivo conditions to get an idea of how the composition would behave in the human body. It is within the level of ordinary skill in the art to manipulate the formulation and pH parameters to achieve the desired release profile over a range of pH environments.

The reference does not teach the AUC values or the Cmax values after administration of sustained release formulation of lamotrigine as in claim 42.

It would have been obvious to one of ordinary skill in the art that the sustained formulation comprising lamotrigine having a Cmax less than the instant release tablet containing the same amount of lamotrigine because Nadkarni teaches that the controlled release lamotrigine, which is designed to avoid excessive Cmax levels will produce lower plasma concentrations, which are reached over a longer period of time. Also, it is obvious to one of ordinary skill in the art that the sustained release formulation comprising the same composition taught by the teachings of Nadkarni and Staniforth will have same release profile and the properties such as AUC and Cmax values.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Umamaheswari Ramachandran whose telephone number is 571-272-9926. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER